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MR 270419

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ExxonMobil Chemical

October 13, 2003

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Document Processing Center (7407M)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention an Toxics,
Environmental Protection Agency
1200 Pennsylvania Avenue, NW,
Washington, DC 20460-0001

Re: Notification under TSCA Section 8(e)

Dear Sir or Madam:
Under the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), ExxonMobil Chemical Company submitted on July 16, 2003, information on the toxicity of a substance described as 1,2-Benzenedicarboxylic acid, di-C6-8 branched alkyl esters, C7-rich (CAS Registry Number 71888-89-6). This substance is currently being manufactured for commercial purposes as defined by TSCA.

The data presented in the submission were from a two-generation reproductive toxicity study in rats. The study protocol followed that described in the U.S. EPA, Health Effects Test Guidelines; OPPTS 870.3800: Reproduction and Fertility Effects (Aug. 1998). The results of the two-generation study are being sent to you in a Final Report titled A Dietary Two-Generation Reproductive Toxicity Study of Di-Isoheptyl Phthalate in Rats and Dated September 10, 2003.

Sincerely,

10/15/03

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FINAL REPORT

Volume 1 of 9
(Text and Summary Tables)

STUDY TITLE

A DIETARY TWO-GENERATION REPRODUCTIVE TOXICITY STUDY OF DI-ISOHEPTYL PHTHALATE IN RATS

STUDY NUMBER

WIL-438002

DATA REQUIREMENT

OPPTS 870.3800
OECD Guideline 416

STUDY DIRECTOR

Donald G. Stump, Ph.D., D.A.B.T.

STUDY INITIATION DATE

October 16, 2001

STUDY COMPLETION DATE

September 10, 2003

PERFORMING LABORATORY

WIL Research Laboratories, Inc.
1407 George Road
Ashland, OH 44805-9281

SPONSOR

ExxonMobil Biomedical Sciences, Inc.
Toxicology and Environmental Sciences, LC 370
1545 Route 22 East
Annandale, NJ 08801-0971

1. SUMMARY

This study was conducted to evaluate the potential adverse effects of di-isoheptyl phthalate on the reproductive capabilities, encompassing gonadal function, estrous cyclicity, mating behavior, conception, gestation, parturition and lactation, in the F_0 and F_1 generations, and F_1 and F_2 weaning, neonatal survival, growth and development. One litter was produced in each generation.

Groups of male and female Crl:CD®(SD)IGS BR rats (30/sex/group) were offered the test article continuously in the diet for a minimum of 70 days prior to mating and continuing until euthanasia. F_0 animals were approximately six weeks of age at the initiation of test diet administration. A concurrent control group received the basal diet on a comparable regimen. Test and basal diet administration continued throughout mating, and through the day prior to euthanasia. Following weaning, F_1 males and females were offered the test article continuously in the diet for a minimum of 70 days prior to mating and continuing throughout mating, gestation and lactation until euthanasia. Target test article concentrations were 1000, 4500 and 8000 ppm (parts per million).

All animals were observed twice daily for appearance and behavior, signs of pharmacotoxicity, moribundity and mortality. Clinical observations, body weights, and food consumption were recorded at appropriate intervals prior to mating and during gestation and lactation. Detailed physical examinations were conducted weekly. All F_0 and F_1 females were allowed to deliver and rear their pups until weaning on lactation day 21. For both generations (F_1 and F_2) eight pups per litter (four per sex, when possible) were selected on postnatal day (PND) 4 to reduce the variability among the litters. Anogenital distance was measured for F_1 pups on PND 1, PND 21 and at the scheduled necropsy; thoracic nipple retention was evaluated for all F_1 male pups on PND 11, 12 and 13. Administration of the test diets to F_1 animals was initiated when animals were 22 days old. Offspring (30/sex/group) from the pairing of the F_0 animals were selected to constitute the F_1 generation. Developmental landmarks (balanopreputial separation and

vaginal patency) were evaluated for the selected F_1 rats. Due to decreased anogenital distance observed in the 8000 ppm group male F_0 offspring (F_1 generation), an additional group of 30 F_1 males, selected from the 8000 ppm group, were retained as a non-treatment recovery (NTR) group. These males were not exposed to the test diet and were not mated, but were assessed for balanopreputial separation (on a comparable regimen with the F_1 generation males) and anogenital distance (on PND 21 and at the scheduled necropsy) to assess the persistence and reversibility of the observed outcome after cessation of exposure. Anogenital distance was also measured for F_2 pups on PND 1. Unselected F_1 pups and all F_2 pups were necropsied on PND 21. The brain, spleen and thymus were weighed from selected F_1 and F_2 pups on PND 21. Each surviving F_0 and F_1 parental animal received a complete gross necropsy following the completion of weaning of the F_1 and F_2 pups, respectively; selected organs were weighed. Spermatogenic endpoints (sperm motility [including progressive motility] and morphology) were recorded for all F_0 and F_1 males, testicular and cauda epididymal sperm numbers were recorded for F_0 and F_1 males in the control and high-dose groups, and ovarian primordial follicle counts were recorded for 10 F_1 females in the control and high-dose groups. In addition, testicular and cauda epididymal sperm numbers were evaluated for F_1 males in the low- and mid-dose groups. Designated tissues from all adult animals, including NTR males, that were euthanized at the scheduled necropsy or *in extremis*, were examined microscopically.

Mean compound consumption (mg/kg/day) for the F_0 and F_1 generations was calculated as follows:

F_0 Generation
Mean Calculated Compound Consumption
(Mg/Kg/Day)[a]

Theoretical Dietary Level (ppm)	Males: Prior to Breeding	Males: After Breeding	Females: Prior to Breeding	Females: Gestation	Females: Lactation
0	0	0	0	0	0
1000	81	50	89	64	162
4500	343	222	406	304	716
8000	623	404	726	532	1289

F_1 Generation
Mean Calculated Compound Consumption
(Mg/Kg/Day)[a]

Theoretical Dietary Level (ppm)	Males		Females		
	Prior to Breeding	After Breeding	Prior to Breeding	Gestation	Lactation
0	0	0	0	0	0
1000	91	50	100	64	168
4500	416	227	462	309	750
8000	764	419	833	543	1360

[a] = Summation of mean compound consumption for the specified interval / Number of periods (weeks, daily intervals) assessed

Test article-related deaths occurred in the 4500 ppm, 8000 ppm and NTR groups, affecting two 8000 ppm group males each in the F_0 and F_1 generations, two NTR males and one 4500 ppm group male in the F_1 generation.

In the F_1 generation, mean gestation body weight gain was statistically significantly reduced for females in the 8000 ppm group during gestation days 0-4; reductions in mean body weights (often statistically significant) were noted for F_1 females in this group throughout gestation and lactation. No adverse effects on body weight or body weight gain were observed in the F_0 females or in the males in either generation.

In the F_1 generation, but not the F_0 generation, several reproductive effects, including statistically significant reductions in male and female mating (8000 ppm) and reductions in fertility (4500 and 8000 ppm; statistically significant at 8000 ppm only) indices, statistically significant reductions in mean sperm production rate and mean testicular sperm concentration (all dose levels) and statistically significant reductions in mean cauda epididymal sperm concentration (8000 ppm) were observed. A number of factors contributed to these effects. For the 8000 ppm group F_1 males, external malformations of the male reproductive organs, including hypospadias (consisting of incomplete closure of the ventral portion of the penis), swelling of the prepuce and undescended testes, were observed. At the *post mortem* examinations of these males, statistically significant

reductions in mean absolute and relative male gonadal and accessory sex organ weights, and associated microscopic degeneration, decreased secretion and/or complete, unilateral or segmental absence of various portions of the reproductive tract were noted. Affected tissues included the testes, prostate, seminal vesicles, seminiferous tubules, vas deferens, coagulating gland and epididymis. Similar macroscopic and microscopic findings were noted in the NTR group males. There was a low incidence of gross testicular findings in the low- and mid-dose group F_1 males, whereas no testicular findings were observed in the control group males. Although the incidence of these testicular findings in the low- and mid-dose groups was not remarkably different from controls, it is assumed that the changes were test article-related, as there was a greater incidence of similar and more severe findings in the high-dose group. In the F_1 generation, the statistically significant test article-related reductions in mean sperm production rate and mean testicular sperm concentration (observed at all dose levels) were accompanied by decreases in mean cauda epididymal and testicular weights in the 8000 ppm group males. Similar findings were not observed in the F_0 generation.

In the F_1 and F_2 litters, developmental toxicity was observed, particularly in male pups. Statistically significant reductions in mean offspring body weight and weight gain were noted for F_1 pups in the 8000 ppm group and F_2 pups in the 4500 and 8000 ppm groups (both sexes). In the F_1 litters, reduced body weights were observed on PND 14 and 21 (statistically significant for females on PND 21), whereas in the F_2 litters, mean body weights were reduced throughout the postnatal period (PND 1-21) and were often statistically significant on PND 14 and 21. For F_1 male pups in the 8000 ppm group, evidence of feminization, including statistically significantly increased thoracic nipple retention on PND 11, 12 and 13, statistically significantly reduced mean anogenital distance (absolute and cube root of pup body weight) on PND 1, PND 21 and at the scheduled necropsy, and delays in (or failure to achieve) balanopreputial separation, was apparent. Delays in (or failure to achieve) balanopreputial separation were also noted in the 4500 ppm and NTR groups, and reduced mean anogenital distance was noted for NTR

males at the scheduled necropsy and for F_2 males in the 4500 and 8000 ppm groups on PND 1; thoracic nipple retention was not evaluated in the F_2 male pups. Test article-related effects on mean offspring organ weights were observed for F_1 and F_2 males and females in the 4500 and/or 8000 ppm groups, and consisted of statistically significant reductions in mean absolute and relative (to final body weight) spleen weights.

Other test article-related microscopic findings were noted for males and/or females in the F_0 and F_1 generations at 4500 and 8000 ppm. These findings included increased incidences of centrilobular hepatocellular hypertrophy, hepatocellular vacuolation (males only) and bilateral chronic progressive nephropathy.

Hydronephrosis (correlating to the gross observation of dilated renal pelvis and to increases in mean kidney weights) was noted for F_1 males in the 4500 and 8000 ppm groups. Additional microscopic findings, including *pars distalis* hypertrophy and/or hyperplasia (correlating to an increase in mean absolute pituitary gland weight) and cystic degeneration of the adrenal cortex, as well as an increased incidence of necrosis of the liver, occurred only in the 8000 ppm group F_1 males.

For both sexes and in both generations, statistically significant increases in mean absolute and/or relative (to final body weight) liver weights, associated with centrilobular hepatocellular hypertrophy, were noted for both sexes in both adult generations at 8000 ppm. Statistically significant increases in mean absolute liver weights were also noted for F_1 females at 4500 ppm. In the F_0 generation, test article-related increases in bilateral chronic progressive nephropathy correlated to statistically significant increases in kidney weight for males at 4500 and 8000 ppm. Test article-related increases in kidney weights for F_0 females in the 4500 and 8000 ppm groups were observed; however, in the absence of microscopic correlates, the increases were not considered adverse. Increases in mean absolute and relative kidney weights were noted for F_1 males in the 4500 and 8000 ppm groups. Although primarily statistically significant in the 4500 ppm group, these

findings were considered to be test article-related and correlated with microscopic renal findings (dilated pelves and hydronephrosis).

Based on the results of this study, a dosage level of 1000 ppm was considered to be the NOAEL (no-observed-adverse-effect level) for parental systemic toxicity of 2-di-isoheptyl phthalate when administered by dietary inclusion to rats. The NOAEL for reproductive toxicity was 8000 ppm for the F_0 generation. The NOAEL for F_1 neonatal toxicity was 1000 ppm. In the F_1 generation, a NOAEL for reproductive toxicity could not be determined due to effects on testicular sperm concentration and macroscopic findings in the 1000 and 4500 ppm groups. Although the testicular sperm concentrations and estimates of daily sperm production in these groups were significantly below the control group values, they were not dose-responsive (the 4500 ppm group values were slightly greater than the 1000 ppm group values) or consistent with other male reproductive data. Specifically, reduced sperm counts were not reflected in reduced gross organ weights or associated with histological changes in these two groups. The epididymal sperm counts in these groups were slightly elevated relative to the control group. In addition, fertility was unaffected in the 1000 ppm group. Thus, the toxicological consequences of this statistical difference are unclear. The NOAEL for F_2 neonatal toxicity was 1000 ppm. There was no indication that the adverse effects of male exposure to 8000 ppm di-isoheptyl phthalate, *in utero* and throughout nursing until weaning, are reversible.